THE FOLLOWING IS A VERBATIM TRANSCRIPT, WITH MINOR EDITS. WE REGRET THAT THE SLIDES TO WHICH DR. CHARNEY ALLUDES ARE NOT AVAILABLE, BUT READERS WILL FIND THAT THE TEXT DESCRIBES THEIR CONTENTS QUITE CLEARLY.

POST TRAUMATIC STRESS DISORDER

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NIMH Constituency Outreach and Education Program Meeting
May 24, 2000

I am going to talk about post traumatic stress disorder today. In part, I wanted to focus on that because I feel it is an underrecognized, underdiagnosed disorder. It is also undertreated. It hasn't been researched enough to develop new treatments. So, it is an important disorder in itself.

In addition, as you know, post traumatic stress disorder is characterized by a severe traumatic event. It turns out if you look at other disorders, particularly depression, that many patients with depression have had severe psychological traumas in their lives that impacts on their illness, the etiology of the depression and also how you might think about treating it.

So, PTSD is an important disorder in and of itself, but psychological trauma as an entity goes across many of the disorders that you are [providing education about].

Abuse is a very big problem in our society. Data from several years ago on the number of reports of child abuse in the United States, going back to about 1994, [shows] there were about three million reported cases of child abuse with one million of those reports being verified. In terms of the type of abuse, 47 percent was neglect, 25 percent physical abuse and 15 percent was sexual abuse.

The problem has not gone away despite a booming economy. More recent data from 1996 shows there were three million cases of reported child abuse. So, it is a very important problem. One of the focuses of research that I am going to be talking about today is, what is the impact of that trauma, both from an emotional perspective, but also what is it doing to the brain.

When you are abused early in life, when your brain is still developing, neurons are being made and pruned to make the brain become mature; what does it mean when there is an enormous amount of abuse during that critical phase of development?

The overall presence of traumatic events in life -- this goes beyond just children -- is very high. For example, the

National Comorbidity Survey showed that the lifetime incidence of experiencing traumatic event severe enough to cause post traumatic stress disorder is more than 50 percent. So, more than one out of two individuals in our country at some point experiences a very severe traumatic event. And it is about the same in males and females – in males, 60 percent, and females, 50 percent.

Approximately 20 to 25 percent of those individuals that experience a traumatic event do develop PTSD. So, if you do a little math, if 50 percent are traumatized, 20 percent get the disease, that means 10 percent of the population have the disease. That qualifies for a very common disorder. Why only 20 percent get it as a result of a severe trauma is another research question.

So, there are underlying vulnerabilities, both in terms of how one was raised, whether the person was abused as a child or not, but there are also genetic risk factors as well. Some factors give people invulnerability, meaning that they can handle a lot of stress without developing the disorder and other genetic risk factors make one more vulnerable. That is another area of research that is ongoing.

What types of events lead to PTSD? Witnessing injury or death, sexual molestation or rape, natural disasters, like fire, hurricanes and so forth. Physical attacks or abuse, being threatened with a weapon and so forth.

Traditionally, people have viewed PTSD as related to combat. It is related to combat, but that is a minor cause in terms of the population as a whole. These other events are more commonly experienced by the general population. So, it is a common condition. It is ranked fifth among all psychiatric disorders. It is more common in women versus men. About 10 percent of American women have at some point in their life met criteria for post traumatic stress disorder.

The reason for that is not known, but it may relate to the type of event. Women are much more likely to be sexually abused, for example. And that is a very severe, obviously traumatic event and the relationship between severity and the development of PTSD is strong. So, while women have about the same number of events, the events that they experience are probably more severe.

This [slide] brings home that point. This indicates the likelihood of developing PTSD in relation to the trauma that one has experienced. So, this large bar here is whether one was held captive, tortured or kidnapped. That is, over 50 percent of individuals who undergo that experience will develop post traumatic stress disorder.

No. 2, though, is rape and that is 50 percent. So, because women are more commonly raped, that probably accounts for why women are more likely to have PTSD than men.

What are the risk factors in terms of developing the disorder? Severity of the event, the duration of the event -- and that is what makes combat such a traumatic event, obviously. When one went to Vietnam, for example, you were there for a year. So, there was not one isolated traumatic event for most soldiers. It was not only severe, but it was a long duration.

The proximity of exposure, the meaning of the exposure, [are risk factors], so that if you witness a plane crash on a TV, that is not the same as witnessing the crash from three miles away, or having the crash occur in your backyard. What is more proximate than a sexual event? So the closer the proximity of exposure, the more likely you are to develop PTSD.

Other risk factors relate to the type of individual you are. What is your genetic [makeup]? Do you have a genetic [makeup] that make you less vulnerable to the effects of stress? Are you more “invincible”, in a sense? What is the family history? It turns out if there is a family history of depression, an anxiety disorder [that could be a risk factor].

The event has to be persistently re-experienced. What is meant by that is that flashbacks, nightmares, the memory of the event do not go away. The event continues to intrude on your regular existence.

There is avoidance of stimuli or situations that remind one of the original event so that you begin to constrict your life. If there was sexual molestation, it will affect the relationships that you develop with partners. Many individuals develop a numbing of general responsiveness. If the event was so horrific and that made you experience a whole lot of emotion, one adaptation is to numb your emotions, to begin to distance yourself from events that arouse emotions. So, that is termed a general numbing.

There are persistent symptoms of hyperarousal, which means your heart might race. You have a very pronounced startle reaction. If there is a loud noise, you are the one that jumps. It is as if your nervous system has been rendered permanently hyperresponsive. That is where we start thinking, well, what is changed. What biological changes have occurred, based on the traumatic exposure?

You have to have the symptoms for more than one month and they have to cause significant distress or impairment. The person experienced, witnessed or was confronted with an event involving actual or threatened or serious injury.

The re-experiencing that I mentioned can occur as recurrent, intrusive, distressing memories, recurrent distressing dreams -- and some individuals have what we call illusions, where they look at something and they, in a sense, misinterpret their surroundings so that they think it is very similar to the original situation. Some people do have hallucinations related to the event. It is not hallucinations that occur like in schizophrenia, in which they may not be related to a specific event. These are. And they have flashbacks.

The general numbing or avoidance relates to avoiding thoughts, feelings or conversations connected to the event, avoiding activities, places or people connected to the event and it is these types of symptoms that result in a great deal of disability. PTSD is a highly disabling condition with a great deal of morbidity and even mortality. The suicide rate is higher among patients with PTSD.

The hyperarousal that I was mentioning relates to problems sleeping, difficulty falling or staying asleep, irritability or outbursts of anger. There can be increased impulsivity, problems concentrating, hypervigilance and an exaggerated startle reaction.

As I was mentioning, the traumatic event is important in [the development of] other psychiatric conditions as well. Among them, depression is the most important. PTSD occurs frequently comorbid with depression. Kenneth Kendler did an analysis in a study of twins, in which he looked at the factors that lead one to have an episode of major depression.

These are some of the factors that lead one to develop a depression; childhood parental loss, a traumatic event. Another factor is perceived parental warmth toward the child; neglect in childhood is a major risk factor for the development of major depression. Genetic factors, lifetime history of trauma. Recent difficulties, stressful life events in the last three months. Social support.

So, you can see most of these boxes that lead to one developing depression are traumatic events, external events. Genetic factors are important but look at all the other factors that are equally important, but not more important.

So, when we think about PTSD and depression and disorders in general as a researcher and also as a clinician, we have to think about the interaction between genes and environs. We are going to learn a lot more about what genes may be related to mental illness. We don't have much knowledge right now, but we will over the next ten years.

We are going to be able to disentangle what are the genetic contributions and what are the environmental contributions and, most importantly, I think we are going to

learn -- and it might seem paradoxical, but we are going to learn what changes we ought to make in one's environment, given the genes that a person is born with.

So, while the genetic findings are very “biological,” they are going to inform how we develop different forms of psychotherapy and psychosocial support in terms of the prevention of illness. [This is critical] because we are a long way from doing gene therapy.

A paper that was published in the Journal of the American Medical Association about a year and a half ago brings home some of the points that I have made: “Clinical characteristics of women with a history of child abuse, unhealed wounds.” Unhealed wounds mean that this experience early in life has very long lasting consequences.

What was important about this study? One, it was large. It looked at almost 2,000 women. It was representative, which means that it wasn't a highly select population in which it is hard to interpret the results in terms of general application.

These were women of varying ages, varying marital, educational and economic status. The settings from which they were drawn were four community-based, primary care internal medicine practices. So, these are women that you interact with in your daily life.

They looked at the incidence of childhood or adolescent physical or sexual abuse. Of these 1,900 plus women, 22 percent (which is an amazing figure when you think about it--one out of every five women), had reported a childhood or adolescent physical or sexual abuse event and most of the time, it was more than one.

There are a lot of findings here, but I just want to point out several. The women that reported this event, or these events, had higher scores for depression, anxiety, somatization, interpersonal sensitivity, which means low self esteem.

They were more likely to be abusing drugs. They had a higher history of alcohol abuse, were more likely to have attempted a suicide, more likely to have a psychiatric admission. They also had higher levels of psychological problems and physical symptoms. So, there was a great deal of morbidity associated with this very common event.

This kind of information has led researchers both in the basic laboratory and in the clinical research laboratory to begin to ask questions about what could events like I have been talking about, do to the brain, do to the functioning of the brain. Can psychological events, severe psychological traumatic events change how the brain operates?

Now, this talk is going to be biologically oriented. If I had asked this question 10 or 15 years ago, people would generally say, the psychological events, change how you feel about yourself. They change your self-esteem. They change your relationship, but they don't really fundamentally change your brain in terms of neurochemistry and structure. But that has changed.

We now know that that is not true. We know it from both what we call basic laboratory studies and clinical studies. I am going to show you how we can translate research from the basic lab, meaning studies in rats or mice or non-human primates, monkeys, and how that gives us important information for how we understand what is happening in human beings.

One question that has been asked in the laboratory is can early experience, in this case, early adverse events exert long term effects on one endocrine system that we know is important. That is the hypothalamic pituitary adrenal system. That is the system that relates to making cortisol -- and we know cortisol is important both in health and disease. It is an important stress hormone.

I am going to illustrate two types of preclinical studies and how they can be important. One group of studies have been done by Paul Plotsky at Emory and Michael Meaney at McGill. They have looked at early maternal behavior in rats, and how that affects the health of the rat pups. They looked at it several ways. They took rat pups that were between the ages of two days and fourteen days, and took the mother away from rat pups for three hours every day. They looked at how those rat pups looked when they got older in terms of how their brains functioned and how their behavior was.

Did taking the mother away for three hours a day, days 2 to 14 of life, have an impact? The answer is "yes," a great impact. I am just going to give you a couple of examples. One type of impact is that if you looked at the rats that were taken away from their mother for three hours a day for 12 days, and [later] you looked at them as adults, a hormone called CRF remains elevated for the life of that animal; this is true even though after day 14, they basically were raised in the same environment as animals that had never been separated from their mother.

[In this slide], if you look at this red bar, that is the amount of CRF in the brain in the animals that were separated from their mother. But this is the amount when they are adults. So, it stays high.

Something has rendered [the CRF)] abnormal and it stays high. In fact, if you look at the amount of CRF in the spinal fluid of these rats when they are adults, it also is very high. That is right here. If you look at these squares, this

is the group that is separated from their mother for three hours a day and the CRF is much higher than in animals that were separated for 15 minutes a day and in animals that were not separated at all. So, this is one example of this one important hormone, CRF, that stays up for the life of an animal, based on a relatively modest separation from their mother.

In another study, we will how maternal behavior was affected [by stress]. This was in monkeys, in which young monkeys were raised under three conditions. In one group of monkeys, the food that was available to them was variable. Sometimes there was a lot of food available. Sometimes there was not. You can see how some of these kinds of experiments might relate to human situations.

So, the mother who is responsible for getting the food for their young monkeys is under stress because she does not know when it is going to be hard to find food versus when food is going to be easily available. [For other groups of monkeys], food was available in a predictable way. So, it was not nearly as stressful. That was the only difference.

When these young monkeys [in the group that had variable food availability] got older, the amount of this hormone in their spinal fluid was elevated; you see the same finding in monkeys basically as you see in the rats.

CRF is corticotropin releasing factor. We all have it. Why is CRF important? This is a peptide that is receiving the most attention right now in comparison to the things that you are usually familiar with, like serotonin and norepinephrine. There is probably more attention now being paid to CRF than those traditional neurotransmitters, because it turns out that CRF is located throughout the brain; and it is also involved in having the pituitary gland release ACTH, which then results in steroids being released, cortisol, and also adrenaline.

If you give CRF to an animal, it turns out that CRF produces in the animal behaviors that resemble anxiety and depression. CRF causes an animal to have less sleep. It causes it to have increased activity, agitation. It causes it to show evidence of anxiety and fear in interaction with other animals and it also creates a situation in animals [show] “learned helplessness,” which is an animal model of depression.

CRF, itself, based on lots of experiments that are too many to review, has been shown to be a peptide that is anxiogenic and “depressed-genic.” If early life events, like just manipulating maternal environment in animals, can cause persistent elevation of this neuropeptide [and] that can produce anxiety and produce depression, that is a problem.

Well, what is the situation in humans? We and others have measured the amount of CRF in humans, who have been exposed to traumatic events -- and years after the exposure and [the results are] just like in the animals.

Twenty-five years after the original trauma [in these people] this peptide is still up. This work has been replicated [by other scientists]. This [slide shows] the amount of the CRF, corticotropin releasing hormonal factor in patients who have PTSD and in normal subjects. CRF stays elevated in the patients with PTSD.

We think that stress causes a chronic elevation of this hormone and it may never go away. We don't know. It turns out if you look in patients with depression, the CRF is much higher in patients with depression. We don't know if these are the patients that have also been traumatized. The reason I am telling you this is it is going to be clinically relevant because the pharmaceutical industry is focused like a laser beam in developing CRF antagonists. We know the structure of the CRF receptor. That is the receptor with which the hormone interacts to have its effect. So, if you can block this receptor with a medication, you will block the effects of CRF. We think that will be a potent anti-anxiety drug and antidepressant. There is research going on at NIMH right now, in Bethesda, looking at this. There is a drug that has been tested in monkeys by [NIMH intramural scientist] Phil Gold that blocks this receptor and several companies have now got drugs in development that block this receptor.

[One company] had a drug that [was tested in] patients and worked. These were patients with depression and anxiety and it worked very well. Unfortunately, that particular compound caused elevation of enzymes in the liver. So, they had to go to another backup compound, but there was what we call proof of principle, which means it looks like this could represent a new class of medication.

So, that is one system that is rendered abnormal [by stress]. There is another system that has been rendered permanently or at least chronically abnormal and that is the brain adrenaline system. The center of the brain adrenaline system is called the locus ceruleus and that is found in the brain stem.

In those rats that I was telling you about that got separated from their mother, if you look at the firing of the adrenaline neuron in the brain [and compare]the animals that were separated from their mother and the control animals, the adrenaline system turns on too easily [in the rats that] had undergone this separation from their mother early in life.

It turns on too easily when they are adults. It doesn't go away. You can study the adrenaline system in people,

almost the same as you can study it in laboratory animals. You can study how the adrenaline system is regulated and the way you can study it is to give a medication, a single dose of a drug, called yohimbine, which turns on the adrenaline system. The mechanism is not that important for now but we know how it does it. It blocks a receptor that tends to inhibit the adrenaline system. So, it unleashes the system by blocking this receptor.

So, researchers have been interested to look at how the adrenaline system is regulated in patients in whom we think adrenaline might be abnormal. We can do that by looking at the effect of a single dose of this medication. It turns out in patients who had PTSD as the result of an event 20 years ago, if you give them placebo and measure any kind of symptoms they are reporting, there is no effect.

If you give a single dose of this drug in a healthy volunteer it does nothing. They can't tell the difference from placebo. But if you give them the drug that turns on adrenaline, even a little bit, it produces a return of symptoms for about 60 minutes. Their adrenaline system is hyperreactive years after the original trauma.

We can measure the amount of adrenaline in the patients with PTSD and healthy subjects, and the amount of adrenaline that is released is threefold higher in the patients with PTSD. It turns out these are the same patients that have the elevation in that peptide I was telling you about. You can also more directly look at the brain adrenaline system by doing PET scanning, OR positron emission tomography, where you can look at metabolism in the brain.

This [slide shows] the function of the adrenaline system in [certain] parts of the brain. Without getting into the details, you can see that the pattern is extremely different in patients and normal volunteers. The adrenaline system is rendered abnormal.

This also may have a clinical implication. PTSD, and in many cases, depression [in people whose depression was those associated with a traumatic event],is in a sense a disorder of memory. The event does not get out of your brain. You can't get rid of it. Now, there are events in each one of your lives that you can remember vividly. Some of them are traumatic and some of them are positive, but you can remember it like yesterday.

If you had a horrific event, you will remember it like yesterday and it will keep coming back; and that is the disorder. So, if we could develop a way of preventing horrific events from being encoded in the brain so that they are essentially <u>intelligible,</u> then we might have a treatment.

Preclinical work has suggested that one of the ways that we remember things is by stimulating a particular receptor in the brain that involves adrenaline, that adrenaline is hitting the beta receptor in the brain and that is why we encode the memory. You undergo an event. Adrenaline gets released. It hits the beta receptor at different parts of the brain and the memory gets encoded.

What if you intervene there in a way that you still remember it but it is not as encoded? Well, to begin the story, there was an interesting experiment conducted in healthy volunteers by Larry Cahill and Jim McGaugh. What they did is they took a group of healthy subjects, a couple of groups of healthy subjects and they told them a story and the story had neutral elements to it and aversive elements to it.

The neutral element was basically that a mother and a child were going to visit their father in a hospital -- he worked there -- like for lunch or something like that. The horrific or emotional element of the story is that when the mother and the child were crossing the street, the boy got hit by a car and was taken to the emergency room of that hospital.

Now, one group of the healthy subjects got a placebo pill before they heard the story and another group got propranolol, a beta blocker, which is used for hypertension. It is used for rapid heartbeat, but it blocks the beta receptor. Then they came back a week later and they got a memory test, a surprise memory test. They were asked, what do you remember about this story? They didn't know it was going to be a memory test.

The group that got the beta blocker, the propranolol, did not remember as well the sad or stressful parts of the story, compared to those who got placebo. That was expected, based on the animal work, that if you block adrenaline from reaching the beta receptor, it might impair, not eliminate but impair severe memories.

That is what they found and this has been replicated. An opposite experiment was done in which instead of blocking adrenaline, we increased adrenaline by giving yohimbine, but did the same thing, told the story and gave a memory test. If you look at the memories, if the patient has got increased adrenaline, they had increased memory.

So, this has led to the idea that when adrenaline is increased at the time of a trauma, it hits the beta receptor and you remember it. Maybe it doesn't go away. What if you gave a beta blocker, which is a safe medication? It has been around for 30 years. What if you gave the beta blocker right after the trauma? If you gave it in the emergency room to a woman who had been raped, for example, or somebody who had been in a horrific car accident, gave a beta blocker for a

couple of days, would that prevent the development of disorder? We don't know. But there are some data that propranolol might be helpful in traumatized children, and there is now research going on giving beta blockers shortly after individuals have been exposed to trauma, to see if it would be a preventative treatment.

So, I have been talking about chemistry, that stress alters the chemistry of the brain. I have given you two examples, that stress alters that peptide CRF, which may have clinical implications; researchers are developing a CRF antagonist. Stress alters adrenaline and we can alter adrenaline. That might affect the progression or the development of a disorder.

Does stress alter the structure of the brain, more than chemistry, actually the structure of the brain? This [quote] is taken from an article written by Robert Sopolsky who essentially said, yes, stress is actually bad for the structure of the brain. What was that based on?

Part of it actually was based on his own work. He is a professor of biology at Stanford and years ago he looked at monkeys that had been under a lot of stress, mainly male monkeys in this case. They went to postmortem and he looked at the hippocampus. The hippocampus is a part of the brain that is very much involved in learning and memory and emotional regulation.

He found that the hippocampus of monkeys that had been under a lot of stress had a loss of neurons. This is psychological stress. This is not physical stress. There were less neurons in the various regions of the hippocampus, including what we call CA1, CA3 and CA4. Through a series of experiments, he worked out what might be doing that.

High levels of cortisol can damage the hippocampus. Cortisol goes up under stress. High levels of glutamate, which is an amino acid, can damage the hippocampus. That led to the question, does this occur in people as well as monkeys? In people undergoing severe stress, could there be a loss of neurons in the hippocampus? We can't take a brain biopsy [in a living person] and look at the number of neurons in the hippocampus, but we can do a magnetic resonance image, MRI. And we can look at the size of the hippocampus. We can measure its volume.

It is cruder than directly looking at the hippocampus, but now four different [research] groups have shown that the size of the hippocampus is smaller in patients with PTSD versus control subjects. It is also smaller in patients with severe depression. [Slides showing brain scans]. Same kind of scan here. That is the normal size and that is the smaller size.

This has been replicated. We found it all sorts of abuse. This [slide shows brain scans of] individuals, women who had been abused sexually before the age of seven; they were studied as adults and their size of their hippocampus on both sides is reduced. And when we use a PET scan and we look at the function of the hippocampus, does it turn on when you present a memory task to these women? The blood flow to the hippocampus at baseline is not different, but when you ask the subject to perform a task, in the healthy subjects the hippocampus activates, but in the PTSD patients there is no activation. That is consistent with the loss of volume.

This is work that is just emerging over the last few years, but it looks like the hippocampus, just as in laboratory animals, has altered its structure, based on severe psychological stress. Very recently, we have been able to start understanding how could that actually happen.

This is work by Elizabeth Gould at Princeton. She discovered that in adult animals new cells are being made in the hippocampus. Now, that was a revolutionary finding, because we were taught that once you became an adult, nothing new was happening in your brain, except bad things, basically. But she found that new cells are being made. It is called neurogenesis. And others have now been looking at what regulates the making of new cells in this very important brain structure.

Well, one thing that regulates it down, meaning it reduces the making of new cells, is stress, psychological stress. Basically, what you get if you took a monkey and took another monkey that was an intruder and looked at the stress of the monkey that was faced with the intruder monkey, just for one hour, the making of new cells in the hippocampus dropped about 40 percent.

So, psychological stress reduces the making of new cells. On the other hand, they found that you can do the opposite. You can enhance the making of new cells. Learning enhances neurogenesis in adult animals. So, that has a lot of positive implications beyond even psychiatry. It means an enriched environment in which learning is continually a task -- and you can think of the implications of this for the elderly in nursing homes -- an enriched environment increases the making of new cells in the hippocampus.

The hippocampus is critical to learning and memory. In fact, it goes down in Alzheimer's. So, here, you are seeing emerging importance of the environment, getting back to my original environment/gene interaction, that environmental events can have fundamental effects on structure and function of the brain.

Lastly, it turns out that the medications that we now use to to treat depression [SSRIs] increase serotonin and [it has been assumed] that is how it works. These drugs do a lot more and maybe the increasing of serotonin is not the primary way it actually works. Ron Duman(?) at Yale looked at a variety of different types of antidepressants that affect norepinephrine or adrenaline, or affect serotonin, and all of these drugs increase the making of new cells in the hippocampus.

So, maybe one of the ways these types of drugs work is they act as a tropic factor, a neurotropic factor. They help the brain respond to stress, reverse the effects of stress by increasing the making of new cells in critical areas of the brain that involve the regulation of emotion. So, let me end with this last quote by Solomon from 1987. This is one of the take-home messages.

"Traumatic experiences scar the traumatized individual, weakening their resilience to future stress. Further, even when individuals seem to have resolved their reaction to trauma, heightened vulnerability that is easily reawakened often ensues. It appears that even when…" -- she was talking about combat, but this is a more general statement – "PTSD remits or on the other hand persists and evolves into a more stable form, the afflicted person may become highly sensitized to stress in general. He or she is permanently altered, harboring the potential for a future response on reexposure."

Well, we do know that individuals can be permanently altered. That is what I have been trying to tell you today. On the other hand, recent findings suggest strategies to reverse that, whether it is a CRF antagonist, whether it is propranolol, whether it is giving medications that enhance the making of new cells. Our knowledge about the neuroscience, I think, is going to have a great impact not only on PTSD, but other disorders that relate to stress.

Thank you.

[Applause.]

Time for a couple of questions.

AUDIENCE: My question is does it work with purely cerebral learning, like history, as opposed to something that is involved with basket weaving, where it is motor --

DR. CHARNEY: Well, good -- you probably didn't realize why that was going to be a good question. It turns out when they looked at what elements of the enriched environment in the mice were responsible for the making of new cells, the biggest factor was running, running on the spinning wheel. That enhanced the making of new cells in the hippocampus. So, you can think about all the implications of that.

The original study, the first study that I showed, where it said "Learning," that was learning [but] the motor aspect of the learning was not critical. So, it is both.

AUDIENCE: Are people like monkeys in that stress reduces that production [of cells] or is there any [evidence of making new cells]?

DR. CHARNEY: [To the first question],that we don't know yet. We know that neurogenesis takes place in humans. That we do know. That was a rather sad experiment, not sad in that it was a failed experiment or it was unethical, but the way they could measure neurogenesis in humans is that there were individuals who were dying of brain cancer and the label that they used to monitor the cancer is the same label that you can use to monitor neurogenesis. So, they gave this label to patients dying of brain cancer and found that there were new cells, not cancer cells, but new cells being made even in these older humans. So, it is occurring in humans. We don't know yet whether it is regulated exactly the same way.

AUDIENCE: -- have they talked about the possibility of using -- testing those levels for diagnosis?

DR. CHARNEY: The problem is that the only way they can measure CRF is a spinal tap. So, we can do it and we do it for research, but I don't think it will be a popular diagnostic [tool].

AUDIENCE: You talked about propranolol, giving it immediately after a traumatic event. Is there any [research] about chronically abused children or combat-related, PTSD, things that would be chronic and long term [in which they are] giving the [beta] blockers?

DR. CHARNEY: It probably won't work as well because the memories are already there and encoded. This [use of propranolol] won't make it that you don't remember it at all. It won't produce amnesia, but it is to lessen the degree of encoding. It is probably too late for propranolol [in people with PTSD].

AUDIENCE: Unless I misunderstood, when you were going over the CRF level in the rats, those that were separated from their mothers for long periods of time had very high levels. Those that were separated for a shorter period of time had the lowest and those that were with their mothers all the time had in between so that those with the mothers had a higher level than those who were separated for a short period of time.

DR. CHARNEY: That is a good observation but numerically while one was slightly higher than the other in terms of 15 minutes per se, no, it wasn't significant. It wasn't statistically significant. So, there is not a real difference.

AUDIENCE: It doesn't mean that children should be separated from their mothers.

DR. CHARNEY: I wouldn't recommend it. Well, 15 minutes a day, that is all right. Good for the parent.

What I didn't tell you, which actually makes it more complicated, it turns out that one of the things that happened here is that the mother when she comes back -– after she has been separated from her rat pup for three hours -- she forgot how to mother. So, it is not the three hours. It is the fact that she is separated for three hours, she comes back, and she doesn't mother well. When they took foster mothers, who had always been with one rat pup or another and they gave those mothers to the [pups] that have been separated for three hours, there was no effect.

The point is that this is a maternal problem here in part. Maternal separation is bad, but it is that the mother forgets how to mother after being separated for three hours. So, it is even more complicated.

AUDIENCE: -- [Researchers] are currently testing high doses of DHEA, which the body uses to make cortisol, to deal with autoimmune disorders. Is it possible that higher levels of cortisol [produced] by the use of a substance such as this could make a difference in the body's ability to regulate depression or the CRF still primary?

DR. CHARNEY: We think both cortisol and CRF have effects that probably are independent. So, CRF has a primary effect. DHEA actually diminishes the effect of cortisol. It doesn't make cortisol. It diminishes the effect so that DHEA can be used to counteract the effects of high levels of cortisol. You can get DHEA in health food stores, for example. It is released under stress. It probably is positive. It is probably a positive adrenal steroid, meaning that it diminishes the effects of stress, but we don't know yet in controlled studies whether it will be a real treatment for an anxiety disorder or depression, but it is being researched.

AUDIENCE: The other question I have is that there is brain loss in schizophrenia [according to]the research that we have seen. Many of the people that we serve are treated for schizophrenia with the new antipsychotics, but they are not treated with drugs such as Prozac or another antidepressant concurrently because they don't want to take the extra medication. But if I read this research right, it may be in their best interest to take one of the newer antidepressants to help them learn and compensate somewhat for the intellectual functioning loss [resulting] from years of the disease.

DR. CHARNEY: What we can say here is that stress is affecting the hippocampus and learning can enhance the

function of the hippocampus and that some of these antidepressants can increase the making of new cells in the hippocampus. We don't know if in a patient with schizophrenia, which has its own etiology and pathology, whether a drug like Prozac will enhance cognition and learning and memory.

In fact, we know it doesn't have a major effect. So, probably the cognitive difficulties in schizophrenia are [due to] a different mechanism than I described here. We are going to need another approach…

END.